AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 04: Dementia (Including Alzheimer's Disease)

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 4 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to help determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern the topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the three topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before May 16, 2013, in this priority area; *and* (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Fourteen topics in this priority area were being tracked in the system as of May 18, 2013.) For the Potential High-Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). Topics in this Executive Summary and report are organized alphabetically by class of therapy and then by individual topic within each class. We present two summaries on three topics (indicated by an asterisk) that emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact.

Priority Area 04: Dementia (Including Alzheimer's Disease)

Topic	High-Impact Potential
1. * Florbetapir F18 (Amyvid)-enhanced positron emission tomography (PET) for detection of beta-amyloid plaques	Lower end of the high-impact-potential range
2. * Flutemetamol-enhanced PET for detection of beta-amyloid plaques	Lower end of the high-impact-potential range
3. * Off-label intranasal insulin for treatment of Alzheimer's disease	Moderately high

Discussion

Most of the research activity in the dementia priority area focuses on Alzheimer's disease (AD)—its diagnosis and new disease-modifying (rather than symptom management) treatments in development.

The National Institute on Aging (NIA) describes AD as progressive and irreversible, gradually destroying memory and cognitive ability. AD is the most common cause of dementia, a group of brain disorders that cause progressive loss of intellectual and social skills to the point of interfering with daily life, according to the Mayo Clinic. They describe primary features of AD as the presence of amyloid plaques and neurofibrillary tangles in the brain and disconnection among neurons in the brain, according to NIA. Symptoms are typically not evident in early, preclinical AD; however,

toxic changes begin to occur, such as abnormal deposits of proteins and less efficiently functioning neurons. Eventually, damage spreads to the hippocampus, the region of the brain responsible for forming memories. In the final stages of AD, brain damage is widespread and brain tissue has shrunk significantly, according to NIA. The Alzheimer's Association indicates that the cause of AD is unknown and that researchers think it results from some combination of genetic, lifestyle, and environmental factors that affect the brain over time.

According to the Alzheimer's Association, 5.2 million people in the United States have AD in 2013. An estimated 11% of people aged 65 years or older and 32% of people aged 85 years or older have AD, although a definitive diagnosis can be made only postmortem upon examination of the brain. AD is the sixth leading cause of death in the United States, according to the Alzheimer's Association.

Much research into AD's causes has focused on two hallmark structures found in the brains of patients with AD: amyloid plaques and neurofibrillary tangles. Amyloid plaques are thought to disrupt and/or damage neurons in the brain. Neurofibrillary tangles may cause cell dysfunction and eventually cell death. Other researchers point to inflammation as a possible cause of the progressive cell death seen in the brains of patients with AD.

In this report, we discuss two new imaging agents closest to diffusion out of a class of six or seven similar positron emission tomography (PET) radiopharmaceuticals in development that are intended to aid in detecting beta-amyloid plaques that many think are associated with AD. Earlier diagnosis could enable earlier intervention for care planning by families and elder caregivers, even in the absence of effective treatment to slow or halt disease progression. We also discuss use of intranasal insulin for treating AD because some researchers think insulin may play a role in cognitive deficits observed in AD.

The search is on for ways to definitively diagnose AD and for drugs, biologics, and alternative or complementary interventions that modify the disease or better manage symptoms to keep patients as independent as possible for as long as possible. The Horizon Scanning System is tracking several drugs in late-phase development.

Positron Emission Tomography (PET) Imaging Agents for Detection of Beta-Amyloid Plaques

- **Key Facts**: Two imaging agents intended for use with PET emerged as interventions with potential for high impact, one of which became commercially available in 2012, and the other of which remains in clinical trials. Flutemetamol F18 (GE Healthcare division of General Electric Co., Fairfield, CT) and florbetapir F18 (Amyvid™, Avid Radiopharmaceuticals subsidiary of Eli Lilly and Co., Indianapolis, IN) are intended to aid detection of beta-amyloid plaques and possible diagnosis of AD.

  Both agents are labeled with an isotope of fluorine (F18), which allows detection by PET scanning when injected intravenously into the patient during PET. Flutemetamol binds specifically to beta-amyloid protein, which is a major component of the amyloid plaques that are considered a hallmark of AD pathology. The flutemetamol developers believe it will be able to differentiate early stage AD from absence of AD based on the increased uptake of the compound by nascent amyloid plaques in patients developing AD. Florbetapir is said to be highly specific in binding to beta-amyloid plaque aggregates and does not bind to tau, synuclein, or other targets. These agents are intended to be used in similar capacities and serve to generate images that highlight areas of high tracer uptake. After image reconstruction, the physician interpreting the images makes a binary assessment (positive or

negative) of whether beta-amyloid plaque is present. Flutemetamol has completed a U.S.-based phase III trial, while another phase III trial is ongoing. A new drug application for flutemetamol was submitted to the U.S. Food and Drug Administration (FDA) in January 2013. FDA approved Florbetapir for marketing in 2012. At this time, the U.S. Centers for Medicare & Medicaid Services does not cover beta-amyloid PET imaging for AD, but it opened a National Coverage Analysis process for "Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease" in October 2012. A Medicare Coverage Advisory Committee met in January 2013 to discuss the evidence and voted (scale of 1–5) on the level of confidence members had in the available evidence. The vote yielded a below-average score. Medicare's proposed decision memo date is July 9, 2013.

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) did not find any policies that include coverage.

- **Key Expert Comments**: Overall, the experts commenting on these agents agreed that F18 imaging agents have potential to fulfill the unmet need associated with being able to diagnose AD, but because no disease-modifying treatments are available, some experts were uncertain about the degree to which this would actually improve patient health outcomes. On the other hand, some thought that knowing that a patient has AD could aid planning for patients in terms of patient safety and care.
- **Potential for High Impact**: Lower end of the high-impact-potential range

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

- **Key Facts**: Insulin delivered intranasally is being investigated for treating AD and might have potential to modify the disease's rate of progression. This approach is based on research findings that suggest that insulin plays a role in cognitive deficits observed in AD. Insulin receptors and insulin-sensitive glucose transporters, which regulate energy metabolism in the central nervous system by mediating glucose uptake in cells, are colocated in brain structures that are involved in memory and have been shown to be compromised in patients with AD. The rationale for using intranasal delivery is based on concerns that delivering insulin via other routes (e.g., intravenously) could adversely alter patients' blood glucose levels. This theory is being explored by several research institutions, rather than by insulin manufacturers. In completed and ongoing clinical trials, several methods have been used for ensuring intranasal delivery, including needleless nostril syringes, a nasal drug electronic atomizer device, and nasal spray bottles. Because insulin is not approved for treating AD, its use for AD is considered off label.
- **Key Expert Comments**: Experts agreed that, in theory, an affordable, widely accessible, noninvasive, and easily administered therapy, such as this might improve patient health and also realize dramatic long-term health care cost savings in AD care. Experts stated that their enthusiasm is predicated on an assumption of efficacy in insulin's potential to modify the AD progression rate and that the preliminary data must be confirmed by larger trials.
- **Potential for High Impact**: Moderately high

Dementia (Including Alzheimer's Disease) Interventions

Positron Emission Tomography (PET) Imaging Agents for Detection of Beta-Amyloid Plaques

Unmet need: Currently, a definitive diagnosis of Alzheimer's disease (AD) can be made only by postmortem examination of the brain. Premortem clinical diagnosis of AD, particularly during the disease's early stages, is not straightforward, especially because many other conditions can cause symptoms that mimic AD. An unmet need exists for ways to help clinicians diagnose AD because even in the absence of effective treatments, a diagnosis could provide useful information to patients and their families for monitoring patient welfare. One previously developed PET tracer, 11C-labeled beta-amyloid ligand Pittsburgh Compound B (PIB), has been investigated for this purpose because it binds specifically to beta-amyloid protein, a major component of the amyloid plaques that are characteristic of AD pathology. However, this agent has limited practicality in clinical use because it has a short half-life and cannot be transported to centers unable to generate it onsite.[1] Several agents, purportedly without this limitation, have been or are being developed to aid diagnosis of AD. These agents include: NAV4694, florbetaben, flutemetamol, and florbetapir.[2] This report looks specifically at flutemetamol and florbetapir because they are closest to diffusion.

Intervention: The GE Healthcare division of General Electric Co., of Fairfield, CT, makes flutemetamol, and the Avid Radiopharmaceuticals subsidiary of Eli Lilly and Co., of Indianapolis, IN, makes florbetapir. Flutemetamol is an investigational radiopharmaceutical contrast agent under study for use in PET imaging to measure beta-amyloid plaque AD.[1] Flutemetamol is a thioflavin-D derivative of PIB that has been labeled with a fluorine isotope, which allows detection by PET scanning.[3-5] Its developers hypothesize that flutemetamol will be able to differentiate patients in early AD stages from patients without AD based on the increased uptake of the compound by nascent amyloid plaques in patients developing AD.[6] In performing a PET scan, clinicians inject a small amount of flutemetamol into the patient's bloodstream and use a gamma camera or whole-body scanner to generate images that highlight areas of high tracer uptake.[7,8] Its manufacturer is also developing a software program intended to categorize flutemetamol PET scans into those exhibiting raised and normal beta-amyloid levels.[9]

Florbetapir (Amyvid™) is also a diagnostic radiopharmaceutical intended to detect the presence of beta-amyloid plaque deposits in the brain during PET imaging scans. Florbetapir is labeled with a fluorine isotope, allowing detection by PET scanning. Preclinical studies demonstrated that florbetapir was highly specific in binding to beta-amyloid aggregates and did not bind to tau, synuclein, or other targets.[10,11]

Clinical trials: One U.S.-based phase III trial is ongoing for flutemetamol while another phase III trial has been completed.[12,13] According to a company press release issued in April 2012, a pooled analysis from 4 studies of 49 patients receiving flutemetamol before or after brain biopsy during shunt placement or intracranial pressure measurement and 68 subjects autopsied to determine the presence of brain amyloid pathology demonstrated that "[f]or patients with biopsy tissue samples, the study found that [18F]flutemetamol detected beta-amyloid with a pooled sensitivity of 93 percent and pooled specificity of 100 percent. In autopsied subjects, [18F]flutemetamol showed the ability to detect beta-amyloid with a sensitivity of 86 percent and specificity of 92 percent."[5] Florbetapir was investigated in phase III trials that are now complete.

Regulatory status: In April 2012, FDA approved florbetapir for marketing in the United States.[14] According to the agent's prescribing information, florbetapir is indicated for use with PET imaging as follows:[15]

> [T]o estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other

> causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathologic diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathologic examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.

The prescribing information also notes limitations: a positive florbetapir scan does not establish a diagnosis of AD or other cognitive disorder, and florbetapir's safety and effectiveness have not been established for predicting development of dementia or other neurologic condition or monitoring responses to therapies.[15]

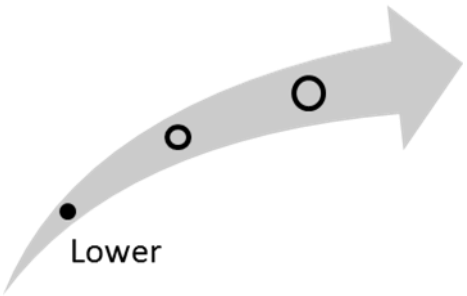
In January 2013, the U.S. Food and Drug administration (FDA) accepted a new drug application for flutemetamol.[16]

The U.S. Centers for Medicare & Medicaid Services (CMS) has established a national coverage determination (NCD) for "Positron Emission Tomography (PET) Scans." The most recent version of the NCD (March 2013) indicates that CMS reimburses only for the use of four radiopharmaceutical tracers (i.e., ^{18}F-fluorodeoxyglucose, rubidium-82, nitrogen-13, and ^{18}F-sodium fluoride) for various indications.[17] All other tracers need to undergo a national coverage analysis process (i.e., evidence compilation, review, public comment period, and final decision memorandum) to render a coverage decision. In October 2012, a national coverage analysis was opened: "Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease." The Medicare Evidence Development and Coverage Advisory Committee convened on January 30, 2013, and voted "low to intermediate confidence" in response to whether available evidence was adequate to determine whether PET imaging of brain beta-amyloid changes health outcomes (improved, equivalent or worsened) in patients who display early symptoms or signs of cognitive dysfunction.[18] A proposed decision memo was expected in July 2013. Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 2 plans with no policies and 9 plans that deny coverage. Plans typically classify PET imaging agents for AD indications as investigational and policies therefore do not cover it.[19-27]

Clinical Pathway at Point of This Intervention

After a patient initially presents with mild cognitive impairment, a physician performs a clinical examination to differentiate mild cognitive impairment caused by incipient AD from mild cognitive impairment caused by any number of other conditions.[28] PET imaging performed with these imaging radiopharmaceuticals would be used to rule out the presence of pathologically significant levels of beta amyloid in the brain and help clinicians differentiate AD from other forms of dementia.

Figure 1. Overall high-impact potential: positron emission tomography (PET) imaging agents for detection of beta-amyloid plaques



Overall, the experts commenting on this intervention agreed that these imaging agents have the potential to fulfill the unmet need associated with AD diagnosis, but because no disease-modifying treatments for AD are available, some experts were uncertain about the degree to which this intervention would actually improve patient health outcomes. On the other hand, some experts thought that having the diagnosis would enable planning for patient safety and care. Experts noted that because PET is a well-established technology, these agents would not cause dramatic changes to health system operations. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

One group of experts (6 people) with clinical, research, and health systems backgrounds offered perspectives on flutemetamol, and a different group of experts (8 people) offered perspectives on florbetapir.[29-42] Although each imaging agent received comments from different groups of individuals, all experts described the agents as having similar potential for impact on the health care system. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: These experts strongly agreed that an important unmet need exists for an effective diagnostic tool for AD. The theory underlying the use of these isotopes in PET scans to meet this unmet need is credible, according to the two groups of experts. They noted that both agents established the validity of PET for this application and the viability of this particular isotope in binding to beta amyloid.

Overall, experts commenting on these interventions agreed that these imaging agents have potential to fulfill the unmet need associated with AD diagnosis, but because no disease-modifying treatments for AD are available, experts were uncertain about the degree to which this intervention would actually improve patient health outcomes.

Health care delivery infrastructure and patient management: Because PET scanning is an established procedure at many facilities, implementing these imaging agents would not bring extensive changes to staffing, infrastructure, or health care processes, the experts generally believe. Some experts did note, however, that although administration of these agents would not require much of a learning curve for clinicians (because their administration is similar to that of other imaging agents), learning to read the images produced by the scan would require some training. Image-interpretation issues (i.e., how the images are interpreted) raised in the published literature after we received expert comments on these agents further emphasize this concern.

One major theme that emerged from expert comments is that no disease-modifying therapy for AD is available. Underscoring this point, most experts thought that these agents, if approved, would have a very minor impact on clinical patient management. An earlier diagnosis could, however,

allow clinicians to start patients on symptom-targeted therapy while symptoms are less pronounced and might give patients and families more time to plan together for future care. Most experts commenting on these imaging agents agreed that the greatest potential impact could be for differentiating AD from other diseases. Because clinicians have no tools to provide a definitive AD diagnosis, this technology has potential to alter the diagnostic pathway for AD.

In terms of cost, most of the experts pointed out the obvious increase in short-term expenditures that PET requires, but some experts noted that early detection might reduce costs associated with AD treatment in the long term. The potential long-term savings might be realized through a variety of mechanisms, experts commented; mechanisms include improved health outcomes (through earlier treatment of either AD or other conditions, if this test is able to rule out AD), reduced need for long-term care, and avoided use of ineffective therapies for incorrect diagnoses.

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

Unmet need: According to the U.S. National Institute on Aging, currently available pharmacotherapies indicated for use in patients with AD treat only the disease symptoms; these medications do not change the underlying disease process, are effective for some but not all people, and when they do help, may help for only a limited time.[43] Therefore, an unmet need exists for novel, effective, disease-modifying agents for AD. Intranasal insulin, if proven effective, might be positioned as the first disease-modifying agent for AD.

Intervention: Research has suggested that insulin may play a role in cognitive deficits in AD.[44] Insulin receptors and insulin-sensitive glucose transporters, which regulate energy metabolism in the central nervous system by mediating glucose uptake in cells, are colocated in brain structures that are involved in memory and have been shown to be compromised in patients with AD.[44,45] Additionally, "peripheral insulin abnormalities" (e.g., insulin resistance) have been associated with increased risk for AD, and patients with AD have shown reduced insulin levels in their cerebrospinal fluid.[44] Finally, research has shown that administering insulin intravenously to patients with AD (while maintaining normal blood glucose levels) improves memory in a dose-dependent manner.

In light of these findings, several research organizations have been begun investigating the use of intranasally delivered insulin for treating AD.[44-46] The rationale for using intranasal delivery is based on concerns that delivering insulin via other routes (e.g., intravenously) could adversely alter blood glucose levels.[45] Drugs administered intranasally can be delivered directly to the central nervous system via the olfactory and trigeminal neural pathways at doses low enough to avoid significant systemic effects.[45] Response to intranasal insulin in patients with AD may differ depending on whether patients have the apolipoprotein e4 allele, which is known to be a genetic risk factor for AD; research has suggested that patients with the allele show cognitive response to lower doses of insulin than do patients without it.[44]

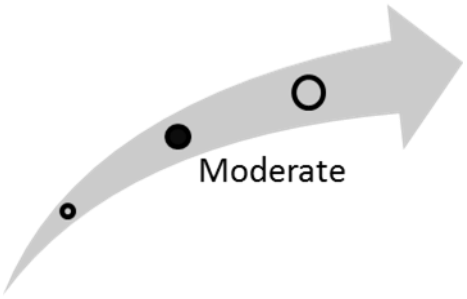
Clinical trials: In completed and ongoing clinical trials on this intervention, several delivery methods have been used, including needleless syringes inserted into alternating nostrils, a nasal drug electronic atomizer device (ViaNase™), and nasal spray bottles.[44,46,47] Various insulin products already approved for use in patients with diabetes have been employed in conjunction with these administration devices, including Novolin R and NovoLog®.[44,46,47] In results reported in 2011, 104 adults with mild amnestic cognitive impairment or mild to moderate AD were given placebo or intranasal insulin for 4 months. Investigators reported that the insulin treatment "improved delayed memory (P <0 .05)," "preserved caregiver-rated functional ability (P <0 .01)," and "preserved general cognition as assessed by the [Alzheimer's Disease Assessment Scale - cognitive subscale] score for younger participants and functional abilities as assessed by the [Alzheimer's Disease Cooperative Study – activities of daily living] scale for adults with AD (P <0 .05)."[46]

Manufacturer and regulatory status: Novo Nordisk a/s, of Bagsvaerd, Denmark, makes Novolin R and NovoLog, and Kurve Technology, Inc., of Lynnwood, WA, makes ViaNase. But insulin manufacturers do not appear to be pursuing development of their products for this indication. Instead, ongoing trials are sponsored by several different research groups, including the University of Kansas (Lawrence), the HealthPartners Research Foundation (Minneapolis, MN), the University of Washington (Seattle), and Wake Forest University (Winston-Salem, NC) in collaboration with Alzheimer's Disease Cooperative Study, a service of the National Institute on Aging and University of California, San Diego.[48-51] Because insulin is not approved for treating AD, use of the drug for AD is considered off label.

Clinical Pathway at Point of This Intervention

Donepezil, rivastigmine, and galantamine are the primary FDA-approved therapies used to treat symptoms of mild to moderate AD, and memantine is approved to treat the symptoms of moderate to severe AD.[43] None of these drugs has been shown to be disease-modifying.[43] Intranasal insulin would likely be used in conjunction with other AD pharmacotherapy.

Figure 2. Overall high-impact potential: off-label intranasal insulin for treatment of Alzheimer's disease



Experts commenting on this intervention agreed that the need for disease-modifying treatments for AD is extremely important and that intranasal insulin is, in theory, an affordable, widely accessible, and easily administered therapy that might realize health improvements and cost savings. This enthusiasm, however, is predicated on the assumption that the agent is efficacious in modifying AD's rate of progression. Experts stated that the available clinical trial data are not yet robust enough to assume efficacy and some were skeptical about the agent's potential to improve health outcomes. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[52-57] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: The need for disease-modifying treatments for AD is extremely important, the experts unanimously agreed, citing both the debilitating nature of the disease and the expected increase in its prevalence as the population ages.

However, several experts expressed uncertainty about intranasal insulin's ability to meet this need. Although most agreed that preliminary trial data are somewhat promising, several experts noted that these results do not yet demonstrate disease regression or slowing of disease progression. Further, only one of two insulin doses used in the trial appeared to be effective, one expert with a research background noted, and another research-based expert commented that it is unclear yet whether the therapy will provide ongoing benefit or whether patients may develop insulin resistance. Finally, another expert with research experience stated that although many researchers are investigating the use of intranasal proteins for brain-related conditions, these attempts have been generally ineffective because of variability in the percentage of the drug that actually reaches the brain or because they do not provide benefit to patients.

Health care delivery infrastructure and patient management: Despite this skepticism about efficacy, most experts agreed that intranasal insulin could have a dramatic impact on the health care system if it were proved to be effective in modifying AD's course, especially because it would be the first agent to treat the underlying cause of AD as opposed to simply addressing symptoms for a

limited period of time. Additionally, because insulin is widely available and relatively inexpensive, it would likely be accessible to a sizable proportion of the population, the experts noted. They thought that the drug's well-known safety profile and long history of use (in diabetes) would increase physician acceptance and adoption of the intervention.

Patient acceptance of the therapy would be widespread because of its ease of use and lack of invasiveness, the experts generally thought. In terms of cost, most experts agreed that the minimal cost of adding insulin to a patient's treatment regimen in the short term would be outweighed by the potentially significant long-term cost savings that would be realized if this agent were to be proved to modify AD progression. If the agent can improve the functional capabilities of patients with AD, experts noted, the sizable costs of their care would also be alleviated, or at least postponed.

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